Atty. Dkt. No. 032026-0527

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Francesco Cerrina, et al.

Title: METHOD AND APPARATUS FOR SYNTHESIS OF ARRAYS OF DNA PROBES

Appl. No.: 09/637,891

Filing Date: 08/09/2000

Examiner: Ardin H. Marschel

Art Unit: 1631

DECLARATION UNDER 37 C.F.R. 1.131

Commissioner for Patents and Trademarks
P.O. Box 1450
Alexandria, VA 22313-1450

I, Francesco Cerrina, state and declare that:

1. I am an inventor of at least Claims 1-3, 5-10, 21-23 and 25-29 of U.S. Patent Application No. 09/637,891, entitled "Method and Apparatus for Synthesis of Arrays of DNA Probes," which claims priority from U.S. Provisional Patent Application No. 60/074,368, filed in the U.S. Patent and Trademark Office on February 23, 1998.

2. Prior to February 11, 1998, I conceived of the subject matter of Claims 1-3, 5-10, 21-23 and 25-29 in the United States. I exercised reasonable diligence to file a patent application for the subject matter of Claims 1-3, 5-10, 21-23 and 25-29 (which I understand is a reduction to practice of the subject matter of Claims 1-3, 5-10, 21-23 and 25-29) from a date prior to February 11, 1998 until February 23, 1998, the filing date of U.S. Provisional Patent Application No.

60/075,641. The original disclosure of U.S. Provisional Patent Application No. 60/075,641 fully supports the subject matter of Claims 1-3, 5-10, 21-23 and 25-29.

3. Exhibit A includes a technology summary form, a document entitled, "A Bench Top Maskless DNA Chip Synthesizer" and an accompanying drawing entitled, "Proposed Mask-less DNA Chip Fabrication" that I prepared with Michael R. Sussman (a co-inventor of the subject matter of Claims 1-3, 5-10, 21-23 and 25-29) and submitted to the Wisconsin Alumni Research Foundation (WARF) as part of an invention disclosure. All dates have been redacted from the documents of Exhibit A to preserve the conception date in confidence. However, I certify that the redacted dates are earlier than February 11, 1998.

4. The subject matter of independent Claims 1-3, 5-10, 21-23 and 25-29 is disclosed in Exhibit A. The drawing in Exhibit A is a copy of the drawing that was filed as FIG. 1 in U.S. Provisional Patent Application No. 60/075,641. The documents and drawing in Exhibit A show the elements of the apparatus recited in Claims 1-3, 5-10, 21-23 and 25-29. Therefore, Exhibit A shows conception of the subject matter of Claims 1-3, 5-10, 21-23 and 25-29 prior to February 11, 1998.

5. Exhibit B is a copy of a letter sent to me by patent attorney Harry C. Engstrom on January 26, 1998, enclosing a first draft of U.S. Provisional Patent Application No. 60/075,641 for my review.

6. Exhibit C is a copy of a letter sent to me by patent attorney Harry C. Engstrom on February 17, 1998, enclosing another draft of U.S. Provisional Patent Application No. 60/075,641 for my review.

7. Exhibits B and C show diligence in reducing to practice the subject matter of Claims 1-3, 5-10, 21-23 and 25-29 from a date prior to February 11, 1998 to the filing date of U.S. Provisional Patent Application No. 60/075,641.

8. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: January 9, 2006 By: ______________________
Francesco Cerrina

A BENCHTOP 'MASKLESS' DNA CHIP SYNTHESIZER

Introduction. With the completion of several genome DNA sequences already in hand (yeast, *E. coli*) and other agriculturally and medically important genomes to be completed within the next 5 years (human, *C. elegans, Arabidopsis*), a new generation of high-throughput analytic schemes for analyzing and using this information are being developed. Foremost among these are DNA 'chips' in which tens or hundreds of thousands of different short DNA oligonucleotides are covalently attached at high density, to a glass surface. The analysis is performed by hybridizing to this chip, any complex DNA sample which has been fluorescently labeled using standard technology. A scanner is used to then measure the intensity of fluorescent light emitted from each of the hundreds of thousand of spots. These chips have an enormous potential for revolutionizing genetic analyses. For example, in a clinical setting, these chips can be used to 're-sequence' the genome of large numbers of human individuals, to determine which genotypes are associated with which diseases. In the laboratory, such chips are used to determine which genes are active and which ones are inactive, in tissues such as cancers or during disease. The immediate impact of these experiments is to identify which proteins are good targets for new drugs or genetic alterations. Even fields as distant as soil ecology or pathology are impacted since it is now possible to simply isolate DNA from any soil or tissue sample and use a microbe 'chip' containing the ribosomal DNA sequence from all known microbes to identify which microbes are present in that sample.

The Maskless DNA Chip Synthesizer. The basic idea is to have a self-contained system capable of synthesizing and thereby fixing the genetic material in specific sites, with a high areal density and with compatibility with fluorescent detection systems. The DNA chip is created using a sequential lithographic process, where areas on the chip are sensitized by illuminating the chip with light usinga specific pattern. Normal phosphoramidate DNA synthesis chemistry is used except that each of the four nucleotide bases (A,T,C, or G) is added with a light sensitive blocking group. This blocking group is removed in a particular pixel when the light is allowed thru at that point.The geometry of the chip is such that each DNA sequence is in the shape of a rectangular array of pixels, typically 10-100 microns in size. Thus, a 1 cm 'chip' pattern containing 90,000 different DNA sequences would contain individual 'pixels' of 300 per side.The number of pixels per pattern is given by the requirement that each be a unique sequence, although some redundancy may be desirable. In current technology, to synthesize 90,000 different DNA sequences of 20 bases long requires 20 x 4 (one for each ofthe four nucleotide bases) for a total of 80 different 'masks'. These masks are similar to the lithographic masks used to synthesize electronic chips and require expensive equipment to make. For long DNA sequences the number of masks becomes large andunwieldy, and since a different mask has to be made for each set of genetic sequences, the expense and development times are prohibitive. *Hence, a maskless approach would be highly desirable.*

Recently, Digital Light Devices (DLDs) have been introduced by Texas Instruments. These devices, based on arrays of micromirrors (each is a square with edges of 10-20), are capable of forming patterned beams of light by turning on or off the mirrors, thus deflecting part of the light off the beam; currently, these chips are available in 640x800 elements (480,000 pixels) within less than 1cm length on each side. Larger arrays are also possible. We are proposing an optical system capable of projecting a demagnified UV (or at any wavelength of choice) image on the chip in real time. By having the DNA synthesis chemistry flowing across the glass on the bottom surface of this chip, hundreds of thousands of different DNA sequences can be built in real time, within a couple of hours. Currently available commercial DNA synthesizers could be easily adapted so that a benchtop 'chip' synthesizer could be built.This unit would create very dense and complex patterns of DNA sequences on chips without expensive and time-consuming masks. Unlike

the current technology, the instrument we are inventing requires no mechanical movement at each cycle of DNA synthesis-the presence or absence of light in a particular pixel during the DNA synthesis cycle is electronically controlled, rather than by the placement of pre-etched lithographic masks.

The optical system could be made completely achromatic (wavelength independent) by using an all-mirror system. Substrates could be glass or silicon wafers, depending mostly on the type of reader used (transmission/reflection). The base retention could be increased by using suitable films of functionalized chemicals (self-assembled materials) or by increasing the substrate effective area (by pre-patterning and etching). The ability to create large numbers of different DNA sequences affixed to glass supports without expensive equipment opens up tremendous possibilities for clinical and basic research utilization. The typical gene contains a unique sequence of four different nucleotide bases which is 1,000-100,000 bases long. The minimum number of different permutations is thus 4 to the 1000th power. Any means by which we can create and sample pieces of DNA within that enormously large dataset will provide advances in diagnostics, cure and treatment which are currently unattainable.

Patterning of the DNA chip. Two approaches are currently considered in the fabricaiton of the DNA chip, and both are adaptations of microlithographic techniques. In a "direct photofabrication approach", a glass substrate is coated with a layer of a chemical capable of binding the bases. Light is applied, deprotecting the OH groups on the base and making them available for binding to the bases. After development, the base is flowed onto the chip and binds to the selected sites. The process is then repeated, binding another base to a different set of locations. The process is simple and effective; using a combinatorial approach the number of permutations increases exponentially. The resolution limit is presented by the linear response of the deprotection mechanism. From the literature, 10 microns pixels appear to be the limiting factors. Because of the limitations in resolution achievable with the previous method, it has been proposed that methods based on photoresist technology be used instead. Here, in the indirect photofabrication approach, the main challenge is to find compatible chemistries, and this was achieved with a two-layers resist system where a first layer of polyimmide acts as a protection for the underlying chemistry, while the top imaging resist is an epoxy-based system.The imaging step is common to both processes, with the main requirement being that the wavelength of light used in the imaging process be long enough not to excite transitions (chemical changes) in the nucleotide bases, that are particularly sensitive at 280nm. Hence,wavelengths longer than 300 nm should be used. At 365 nm we find the I-line of mercury, which is the one used most commonly in wafer lithography. The methods described in the literature are contact or proximity exposure systems, which are inherently difficult to implement. Furthermore, to obtain a large number of bases sequence it is necessary to employ a large number of masks and exposure steps. The integration of patterning and fixing of the bases would provide a definite advantage in terms of manufacturability. The elimination of the masks would add even further benefits.

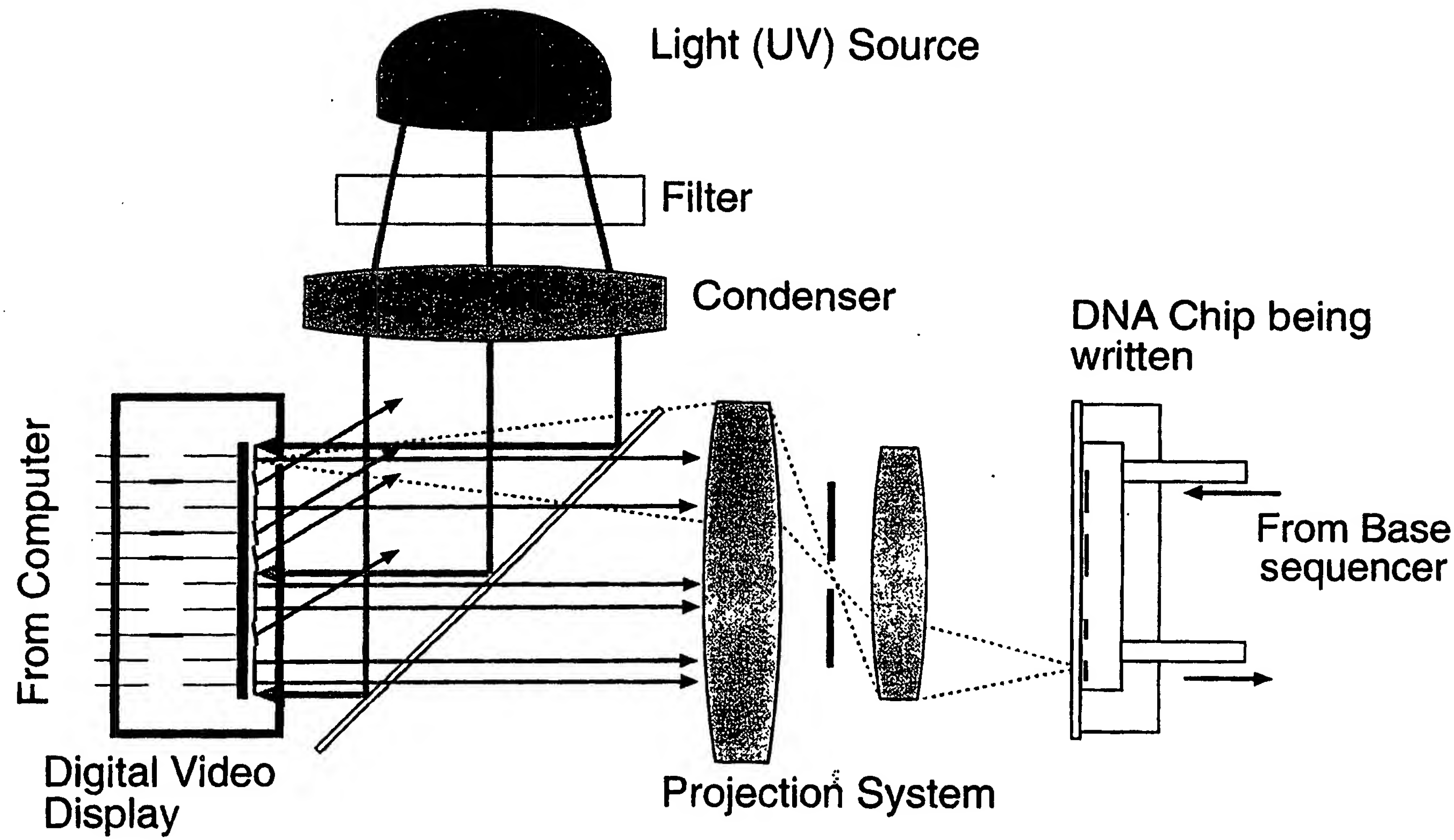
The heart of the new 'maskless' system in our invention is a Texas Instrument Digital Video Display chip (DVD) (also called Digital Micromirror Device, or DMD). This micromachined chip includes an array of micromirrors (typically 10-20 microns to the side) that can be tiltedby applying a digital electronic signal to the chip. When illuminated, the tilted mirrors will direct light away from the central (rest) beam position (see diagram attached) . Thus, the DVD can be used as an image forming system, and are now being developed for use in commercial image projectors for video presentations. In our invention, the DVD chip is illuminated with near-UV light of suitable wavelength and imaged by a reduction system onto the glass (quartz) substrate. Thus, by writing to the chip, an image is formed on the substrate. Since the chips are designed for 800x640 pixels(SVGA), they encode 512,000 pixels and the image is about 2.2 x 1.8 square mm. A larger chip can be madeby multiple side-by-side exposures, or by using a larger DVD (e.g., 1000 x 780). The image can be formed through the quartz substrate, so that there is

no need to move the chip during the sequencing operations. The optics required to image over the field are relatively simple, since the images are large and well away from the diffraction limit; the optics can be designed so that thelight deflected away (10 degrees maximum) falls outside the entrance pupil (typically 0.5 / 5 = 0.1; 10 deg correspond to an aperture of 0.17 > 0.1). Dimensions as small as 0.5 microns should be possible. In order to expose larger fields, a step-and-repeat system may be necessary, with registration marks to align the image and the glass slide. While they would complicate the system, these techniques are well developed. For manufacturing applications, the DVD is located at the object focal plane of a lithographic I-line lens (optimized for 365nm).These lenses typically operate with NA of 0.4-0.5, and have largefield capability (1cm). A particularly appealing approach would bethe combination of a long DVD (with say 2000 elements in one line) with a scanning system (similar to a Micralign). In this case the height of the image is fixed by the height of the DVD, but the width becomes unlimited; as the stage carrying the DNA chip is moved, the mirrors are cycled defining the patterns at each new location. The high bandwidth of the DVD will allow fast scanning rates.

Example of DVD Chip and Resultant DNA Chip Produced

Nx	800 Pixels
Ny	640 Pixels
Size	10 microns per mirror side
Pitch	14 micron spacing
Lx	11200 microns wide
Ly	8960 microns high
Reduction factor	5 (variable, due to optics)
Dlx	2240 microns DNA chip width
Dly	1792 microns DNA chip height
Resolution	2 microns in DNA chip

Proposed Mask-less DNA Chip Fabrication



Confidential and Proprietary

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EXHIBIT B

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January 26, 1998

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Re: Provisional Patent Application--SYNTHESIS OF ARRAYS OF DNA PROBES--WARF-421; 032026:0421; P98077US

Dear Professors Cerrina and Sussman:

Enclosed you will find copies of a first draft of a provisional patent application on the maskless DNA chip synthesizer invention. Please review the provisional application and provide me with any comments, corrections or additions as soon as possible.

The enclosed provisional application does not include claims, which is conventional for applications of this type. Once filed, the provisional application will not be examined by the U.S. Patent and Trademark Office. However, if a regular U.S. application is filed within one year of the filing date of the provisional application, the claims of the U.S. application that are fully supported by the provisional application will be given the benefit of the provisional filing date with regard to intervening prior art. To be able to obtain this benefit, it is essential that the provisional application adequately and accurately describes the invention, that it provide sufficient description to enable any person of ordinary skill to make and use the

invention, and that the best mode known by the inventors for carrying out the invention is disclosed.

A U.S. provisional application can also be used to provide a priority date for foreign applications filed within one year of the provisional application filing date.

The provisional application does not need to be signed by the inventors. However, at least one inventor must be identified in the transmittal documents that accompany the provisional application to the Patent and Trademark Office. It is possible to name additional inventors in the regular U.S. application that is filed based on the provisional application. Because the regular U.S. application would contain claims which define the invention for which patent protection is sought, the inventors named on the regular application would be determined with regard to their contribution to the claims in the application. The provisional application does not include claims, but the subject matter to which the application is directed is generally discussed in the Summary of the Invention section. If you believe that anyone other than the two of you should be named as a coinventor on this provisional application at this time, please let me know. Please again bear in mind that additional inventors may be included on the regular U.S. application when the subject matter to be claimed is more definitely known.

If the invention disclosed in the accompanying provisional application was supported by any government contracts or agency support, please provide the pertinent contract number and other agency funding information to me since that information ordinarily must be supplied to the Patent and Trademark Office with the provisional application.

Please feel free to contact me if you have any questions that you would like to discuss while reviewing the application. My direct telephone line is (608) 258-4207 and my e-mail address is engstrom@execpc.com.

Very truly yours,

Harry C. Engstrom

Enclosures
cc: Marnie A. Matt (w/encls.)
Carl Gulbrandsen (w/encls.)

EXHIBIT C

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Re: Provisional Patent Application–**SYNTHESIS OF ARRAYS OF DNA PROBES**–WARF-421; 032026:0421; P98077US

Dear Professors Cerrina, Sussman and Blattner:

Enclosed you will find copies of a provisional patent application on the maskless DNA chip synthesizer invention. A preliminary set of claims has been included with this draft of the provisional application.

Please review the enclosed provisional application draft and provide me with any comments or corrections that you may have. If the application in its present form is acceptable, I will proceed to file it directly with the Patent and Trademark Office to obtain a filing date as

soon as possible. The provisional application does not require signatures of the inventors before filing.

If the invention in the accompanying provisional application was supported by government contracts or agency support, please provide the pertinent contract number and agency funding information so that the information can be included with the provisional application as filed.

Please feel free to contact me if you have questions concerning the application that you would like to discuss.

Very truly yours,

Harry C. Engstrom

Enclosures
cc: Marnie A. Matt (w/encls.)
Carl Gulbrandsen (w/encls.)

Knorr synthesis [ORG CHEM] A condensation reaction carried out in either glacial acetic acid or an aqueous alkali in which an α-aminoketone combines with an α-carbonyl compound to form a pyrrole; possibly the most versatile pyrrole synthesis. { 'nȯr ,sin·thə·səs }

knot [COMPUT SCI] *See* deadlock. [MATER] A scar on lumber marking a place where a branch grew out of the tree truck. [MATH] In the general case, a knot consists of an embedding of an *n*-dimensional sphere in an $(n+2)$-dimensional sphere; classically, it is an interlaced closed curve, homeomorphic to a circle. [ORG CHEM] A chiral structure in which rings containing 50 or more members have a knotlike configuration. [PHYS] A speed unit of 1 nautical mile (1.852 kilometers) per hour, equal to approximately 0.51444 meters per second. { nät }

knotted yarn *See* knop. { 'näd·əd 'yärn }

knot theory [MATH] The topological and algebraic study of knots emphasizing their classification and how one may be continuously deformed into another. { 'nät ,thē·ə·rē }

knowledge base [COMPUT SCI] A collection of facts, assumptions, beliefs, and heuristics that are used in combination with a database to achieve desired results, such as a diagnosis, an interpretation, or a solution to a problem. { 'näl·ij ,bās }

knowledge-based system [COMPUT SCI] A computer system whose usefulness derives primarily from a data base containing human knowledge in a computerized format. { 'näl·ij ,bāst ,sis·təm }

knowledge engineer [COMPUT SCI] An individual who constructs the knowledge base of an expert system. { 'näl·ij ,en·jə,nir }

Knox and Oxborne furnace [MIN ENG] A continuously working shaft furnace for roasting quicksilver ores, having the fireplace built in the masonry at one side; the fuel is wood. { 'näks ən 'äks·bərn ,fər·nəs }

knoxvillite *See* copiapite. { 'näks·vi,līt }

knuckle [MIN ENG] The place on an incline where there is a sudden change in grade. { 'nək·əl }

knuckle joint [DES ENG] A hinge joint between two rods in which an eye on one piece fits between two flat projections with eyes on the other piece and is retained by a round pin. { 'nək·əl ,jȯint }

knuckle joint press [MECH ENG] A short-stroke press in which the slide is actuated by a crank attached to a knuckle joint hinge. { 'nək·əl ,jȯint ,pres }

knuckle man [MIN ENG] A worker who connects mine cars to and disconnects them from cables and also couples cars into trains. { 'nək·əl ,man }

knuckle pin [DES ENG] The pin of a knuckle joint. { 'nək·əl ,pin }

knuckle post [MECH ENG] A post which acts as the pivot for the steering knuckle in an automobile. { 'nək·əl ,pōst }

Knudsen cell [PHYS CHEM] A vessel used to measure very low vapor pressures by measuring the mass of vapor which escapes when the vessel contains a liquid in equilibrium with its vapor. { kə'nüd·sən ,cel }

Knudsen cosine law [PHYS] A law which states that the probability of a gas molecule leaving a solid surface in a given direction within a solid angle $d\omega$ is proportional to $\cos\theta\, d\omega$, where θ is the angle between the direction and the normal to the surface. { kə'nüd·sən 'kō,sīn ,lȯ }

Knudsen flow *See* free molecule flow. { kə'nüd·sən ,flō }

Knudsen gage [ENG] An instrument for measuring very low pressures, which measures the force of a gas on a cold plate beside which there is an electrically heated plate. { kə'nüd·sən ,gāj }

Knudsen-Langmuir equation [CHEM ENG] Relationship of molecular distillation rate to vapor saturation pressure, solution temperature, and molecular weight during evaporation and no-recycle condensation. { kə'nüd·sən 'laŋ,myür i,kwā·zhən }

Knudsen number [FL MECH] The ratio of the mean free path length of the molecules of a fluid to a characteristic length; used to describe the flow of low-density gases. { kə'nüd·sən ,nəm·bər }

Knudsen reversing water bottle [ENG] A type of frameless reversing bottle for collecting water samples; carries reversing thermometers. { kə'nüd·sən ri¦vərs·iŋ 'wȯd·ər ,bäd·əl }

Knudsen's equation [PHYS] An equation for the amount of gas that flows through a tube in free molecule flow, $q\sqrt{2\pi}\Delta p d^3/\sqrt{\rho}$, where q is the volume of gas measured at unit pressure that flows through the tube per second, Δp is the difference between the pressures at the ends of the tube, d is the inside diameter of the tube, l is the length of the tube, and ρ is the density of the gas at unit pressure. { kə'nüd·sənz i,kwā·shən }

Knudsen's tables [OCEANOGR] Hydrographical tables published by Martin Knudsen in 1901 to facilitate the computation of results of seawater chlorinity titrations and hydrometer temperature readings, and their conversion to salinity and density. { kə'nüd·sən ,tā·bəlz }

Knudsen vacuum gage [ENG] Device to measure negative gas pressures; a rotatable vane is moved by the pressure of heated molecules, proportionately to the concentration of molecules in the system. { kə'nüd·sən 'vak·yəm ,gāj }

knurl [ENG] To provide a surface, usually a metal, with small ridges or knobs to ensure a firm grip or as a decorative feature. { nərl }

koala [VERT ZOO] *Phascolarctos cinereus*. An arboreal marsupial mammal of the family Phalangeridae having large hairy ears, gray fir, and two clawed toes opposing three others on each limb. { kō'äl·ə }

Kobayashi potential [MATH] A solution of Laplace's equation in three dimensions constructed by superposition of the solutions obtained by separation of variables in cylindrical coordinates. { ,kō·bī'yä·shē pə,ten·chəl }

kobellite [MINERAL] $Pb_2(Bi,Sb)_2S_5$ A blackish-gray mineral composed of antimony bismuth lead sulfide. { 'kō·bə,līt }

Kochab [ASTRON] The brighter of the two stars called the Guardian of the Pole in the constellation Ursa Minor. { 'kä·,käb }

Koch curve [MATH] A fractal which can be constructed by a recursive procedure; at each step of this procedure every straight segment of the curve is divided into three equal parts and the central piece is then replaced by two similar pieces. { 'kōk ,kərv }

Koch freezing process [MIN ENG] A process used to sink a shaft through a formation such as clay that will not sustain a shaft; magnesium chloride cooled to about −30°C is circulated through pipes sunk in the ground until the ground is frozen. { 'kōk 'frēz·iŋ ,prä·səs }

Koch's postulates [MICROBIO] A set of laws elucidated by Robert Koch: the microorganism identified as the etiologic agent must be present in every case of the disease; the etiologic agent must be isolated and cultivated in pure culture; the organism must produce the disease when inoculated in pure culture into susceptible animals; a microorganism must be observed in and recovered from the experimentally diseased animal. Also known as law of specificity of bacteria. { 'kōks 'päs·chə·ləts }

Koebe function [MATH] The analytic function $k(z) = z(1-z)^{-2} = z + 2z^2 + 3z^3 + \cdots$, that maps the unit disk onto the entire complex plane minus the part of the negative real axis to the left of $-1/4$. { 'kā·bē ,fəŋk·shən }

koechlinite [MINERAL] Bi_2MoO_6 A greenish-yellow orthorhombic mineral composed of a bismuth molybdate. { 'kek·lə,nīt }

Koehler lamp [MIN ENG] A naphtha-burning flame safety lamp for use in gaseous mines. { 'kā·lər ,lamp }

koembang [METEOROL] A dry foehnlike wind from the southeast or south in Cheribon and Tegal in Java, caused by the east monsoon which develops a jet effect in passing through the gaps in the mountain ranges and descends on the leeward side. { 'küm,baŋ }

koenenite [MINERAL] $Mg_5Al_2(OH)_{12}Cl_4$ A very soft mineral composed of a basic magnesium aluminum chloride. { 'kō·nə,nit }

Koepe hoist *See* Koepe winder. { 'kep·ə ,hȯist }

Koepe shear [MIN ENG] A wheel used in place of a winding drum in the Koepe winder; made up of a cast steel hub with steel arms and a welded rim. { 'kep·ə ,shēr }

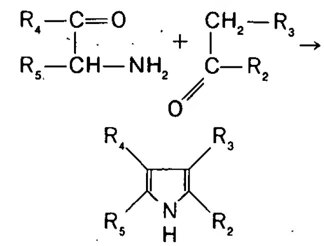
Koepe winder [MIN ENG] A hoisting system in which the winding drum is replaced by large wheels or sheaves over which passes an endless rope. Also known as Koepe hoist. { 'kep·ə ,wīn·dər }

Koepe winder brake [MIN ENG] A device that works directly on the Koepe shear to slow or stop the hoist; can be applied by the engineman's brake lever or by safety devices. { 'kep·ə ¦wīn·dər ,brāk }

koettigite [MINERAL] $Zn_3(AsO_4)_2{\cdot}8H_2O$ A carmine mineral composed of a hydrated zinc arsenate. { 'ked·i,gīt }

Kohler illumination [OPTICS] A method of illumination for

KNORR SYNTHESIS



Equation of the reaction in the Knorr synthesis where an α-aminoketone combines with an α-methylene carbonyl compound to form a pyrrole.

KOALA

The koala, a slow-moving aboreal animal.

the optical microscope used with coiled filaments or other sources of irregular form or brightness; an image of the filament large enough to fill the iris opening is focused on the condenser which is focused so that the image of the iris diaphragm on the lamp is in focus with the specimen, and the lamp iris is opened only enough to fill the field of view; the iris of the microscope is opened only enough to illuminate the back aperture of the objective; no ground glass is used. { 'kō·lər i,lü·mə'nā·shən }

Kohler's disease *See* osteochondrosis. { 'kō·lərz di,zēz }

KOHLRABI

Kohlrabi *(Brassica caulorapa). (Joseph Harris Co., Rochester, N.Y.)*

kohlrabi [BOT] A biennial crucifer, designated *Brassica caulorapa* and *B. oleracea* var. *caulo-rapa*, of the order Capparales grown for its edible turniplike, enlarged stem. { kōl'rä·bē }

Kohlrausch law [PHYS CHEM] **1.** The law that every ion contributes a definite amount to the equivalent conductance of an electrolyte in the limit of infinite dilution, regardless of the presence of other ions. **2.** The law that the equivalent conductance of a very dilute solution of a strong electrolyte is a linear function of the concentration. { 'kōl,raůsh ,lò }

Kohlrausch method [PHYS CHEM] A method of measuring the electrolytic conductance of a solution using a Wheatstone bridge. { 'kōl,raüsh ,meth·əd }

kohm *See* kilohm. { ¦kā¦ōm }

Kohn effect [SOLID STATE] A sharp change in the phonon dispersion curve of a material when the wave-number vector of the phonons corresponds to the diameter of the Fermi sphere, because of the production of standing waves. { 'kōn i,fekt }

Kohoutek's comet [ASTRON] A comet that was discovered on March 7, 1973, at a distance of 4 astronomical units from the sun, and reached a perihelion of less than 0.1 astronomical unit at the end of 1973. { kə'hō·teks ,käm·ət }

koilonychia [MED] Spoon-shaped deformity of the fingernails, which may be familial or associated with a disease, such as iron-deficiency anemia. Also known as spoon nail. { ,kȯil·ō'nik·ē·ə }

koilorachic [MED] Having the lumbar spinal region concave ventrally. { ¦kȯil·ə¦rak·ik }

Kojic acid [ORG CHEM] $C_6H_6O_4$ A crystalline antibiotic with a melting point of 152–154°C; soluble in water, acetone, and alcohol; used in insecticides and as an antifungal and antimicrobial agent. { 'kō·jik ,as·əd }

koktaite [MINERAL] $(NH_4)_2Ca(SO_4)_2 \cdot H_2O$ A mineral composed of a hydrous calcium ammonium sulfate. { 'käk·tə,īt }

kolbeckite [MINERAL] A blue to gray mineral composed of a hydrous beryllium aluminum calcium silicate and phosphate. Also known as sterrettite. { 'kōl,be,kīt }

Kolbe hydrocarbon synthesis [ORG CHEM] The production of an alkane by the electrolysis of a water-soluble salt of a carboxylic acid. { 'kōl·bə ,hī·drə'kär·bən ,sin·thə·səs }

Kolbe-Schmitt synthesis [ORG CHEM] The reaction of carbon dioxide with sodium phenoxide at 125°C to give salicyclic acid. { 'kōl·bə 'shmit ,sin·thə·səs }

Kollsman window [AERO ENG] A small window on the dial face of an aircraft pressure altimeter in which the altimeter setting in inches of mercury is indicated. { 'kōls·mən ,win·dō }

Kolmer test [PATH] A complement-fixation test for syphilis and other diseases. { 'kōl·mər ,test }

Kolmogorov-Arnold-Moser theorem [PHYS] A theorem that oscillatory motions in conservative dynamical systems persist when small perturbations are added to the system. Abbreviated KAM theorem. { ,kȯl·mə'gȯ·rȯf 'ar·nəld 'mō·zər ,thir·əm }

Kolmogorov consistency conditions [MATH] For each finite subset F of the real numbers or integers, let P_F denote a probability measure defined on the Borel subsets of the cartesian product of $k(F)$ copies of the real line indexed by elements in F, where $k(F)$ denotes the number of elements in F; the family $\{P_F\}$ of measures satisfy the Kolmogorov consistency conditions if given any two finite sets F_1 and F_2 with F_1 contained in F_2, the restriction of P_{F2} to those sets which are independent of the coordinates in F_2 which are not in F_1 coincides with P_{F1}. { ,kȯl·mə'gȯ·rȯf kən'sis·tən·sē kən,dish·ənz }

Kolmogorov inequalities [MATH] For each integer K let X_k be a random variable with finite variance σ_k and suppose $\{X_k\}$ is an independent sequence which is uniformly bounded by some constant c; then for every $\epsilon>0$, and integer n,

$$1 - (\epsilon + 2c)^2 \Big/ \sum_{k=1}^{n} \sigma_k^2 \le \text{Prob}\ \{\max_{k\le n} |S_k + ES_k| \ge \epsilon\}$$

and $\frac{1}{\epsilon^2} \sum_{k=1}^{n} \sigma_k^2 \ge$ P

here

and ES_k denotes the expe
i'kwäl·əd·ēz }
Kolmogorov inertial sul
tion of the turbulence spe
(long-wave) part and the
{ ,kȯl·mə'gȯ·rȯf i'nər·sh
Kolmogorov-Sinai inva
variant of measure-preser
preserving transformatic
gorov-Sinai invariant is
entropies of T given each
Also known as entropy
'sī,nī in¦ver·ē·ənt }
Kolmogorov-Smirnov
measure goodness of fit c
critical values exist to t
'smir,nȯf ,test }
Kolosov-Muskhelishvil
express plane strain and p
functions of the comple
are plane coordinates. {
ləz }
komatiite [PETR] A m
content of magnesiu
{ kō'mäd·ē,īt }
Komodo dragon [VE
predatory reptile of the
island of Komodo; it is
to 10 feet (3 meters). {
kona [METEOROL] A
southwest or south-sou
times a year on the soutl
prevailing northeast trac
kona cyclone [METE
clone which forms in
season. Also known a
kona storm *See* kona cy
Kondo alloy [MET] A
nonmagnetic host whic
,al,ȯi }
Kondo effect [MET]
resistance of certain dil
magnetic hosts as the te
Kondo resonance *See*
,rez·ən·əns }
Kondo temperature [
Kondo effect predomir
and host material. { 'k
kongsbergite [MINER
amalgam composed
{ 'kaŋz,bər,gīt }
konig [OPTICS] The
Königsberg bridge pr
ing across seven bridge
ified manner exactly o
this is the original pro
{ ¦kərn·iks,bərg 'brij ,p
Konig's theorem [MA
rem that the minimum
maximum number m
əm }
konimeter [ENG] A
dust as in a cement m
drawn through a jet i
surface; the particles a
əd·ər }
koninckite [MINERAL
posed of a hydrous fer
koniscope [ENG] A
of dust particles in th
{ 'kän·ə,skōp }
Konowaloff rule [PH
that in the vapor over a